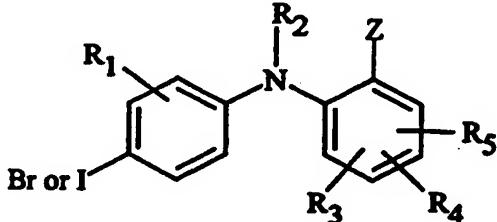




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| (54) Title: 2-(4-BROMO OR 4-iodo PHENYLAMINO) BENZOIC ACID DERIVATIVES AND THEIR USE AS MEK INHIBITORS | | | |
| (57) Abstract | | | |
| <p>Phenylamino benzoic acid, benzamides, and benzyl alcohol derivatives of formula (I) where R₁, R₂, R₃, R₄, R₅, and R₆ are hydrogen or substituent groups such as alkyl, and where R₇ is hydrogen or an organic radical, and Z is COOR₇, tetrazolyl, CONR₆R₇, or CH₂OR₇, are potent inhibitors of MEK and, as such, are effective in treating cancer and other proliferative diseases such as inflammation, psoriasis and restenosis, as well as stroke, heart failure, and immunodeficiency disorders.</p> | | | |
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2-(4-BROMO OR 4-IODO PHENYLAMINO) BENZOIC ACID DERIVATIVES AND THEIR USE AS MEK INHIBITORS

FIELD OF THE INVENTION

This invention provides benzoic acid and amide derivatives of anthranilic acids which inhibit certain dual specificity kinase enzymes involved in
5 proliferative diseases such as cancer and restenosis.

BACKGROUND OF THE INVENTION

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Cancer, for example, is commonly caused by a series of defects in these signaling proteins,
10 resulting from a change either in their intrinsic activity or in their cellular concentrations. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common
15 mutations occur in genes encoding the protein known as Ras, which is a G-protein that is activated when bound to GTP, and inactivated when bound to GDP.

The above mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in
20 most cell types. Defects in this signaling system, especially in the deactivation of the Ras.GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active
25 Ras.GTP for its own activation is the Raf family. These in turn activate MEK, (eg, MEK₁ and MEK₂) which then activates MAP kinase. Activation of MAP kinase by mitogens appears to be essential for proliferation, and constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream

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Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S²¹⁸ and S²²² in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y¹⁸⁵, and a threonine residue, T¹⁸³, separated by a single amino acid. This double phosphorylation activates MAP kinase at least 100-fold, and it can now catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, whether it be another kinase, a transcription factor, or other cellular protein. MEK is also activated by several kinases other than Raf-1, including MEKK, and itself appears to be a signal integrating kinase. As far as is currently known, MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than MAP kinase has been demonstrated to date, and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

This invention provides compounds which are highly specific inhibitors of the kinase activity of MEK. Both in enzyme assays and whole cells, the compounds inhibit the phosphorylation of MAP kinase by MEK, thus preventing the activation of MAP kinase in cells in which the Ras cascade has been activated. The results of this enzyme inhibition include a reversal of transformed phenotype of some cell types, as measured both by the ability of the transformed cells to

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grow in an anchorage-independent manner and by the ability of some transformed cell lines to proliferate independently of external mitogens.

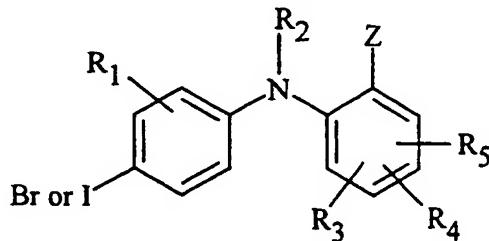
The compounds provided by this invention are 2-(phenylamino) benzoic acid, tetrazole, ester, amide, and benzyl alcohol derivatives, in which the phenyl ring is substituted at the 4-position with bromo or iodo. United States Patent No. 5,155,110 discloses a wide variety of fenamic acid derivatives, including certain 2-(phenylamino) benzoic acid derivatives, as anti-inflammatory agents. The reference fails to describe the compounds of this invention or their kinase inhibitory activity.

10

SUMMARY OF THE INVENTION

This invention provides 4-bromo and 4-iodo phenylamino benzoic acid derivatives which are selective MEK kinase inhibitors and as such are useful for treating proliferative diseases such as cancer, psoriasis, and restenosis. The compounds are defined by Formula I

15



I

wherein:

R₁ is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or CN;

R₂ is hydrogen;

20

R₃, R₄, and R₅ independently are hydrogen, hydroxy, halo, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, nitro, CN, or -(O or NH)_m -(CH₂)_n-R₉, where R₉ is hydrogen, hydroxy, CO₂H, or NR₁₀R₁₁;

n is 0-4;

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m is 0 or 1;

R₁₀ and R₁₁ independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached, can complete a 3-10 member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

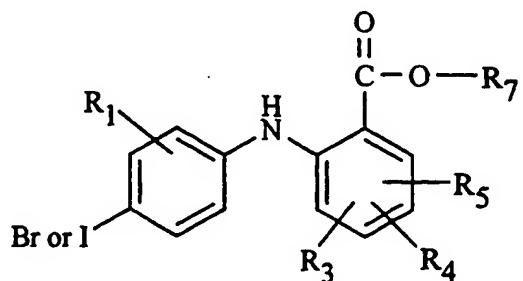
5 Z is COOR₇, tetrazolyl, CONR₆R₇, CONHNR₁₀R₁₁, or CH₂OR₇;

R₆ and R₇ independently are hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl,

10
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{-C}_8 \text{ alkynyl, } \text{C-C}_1\text{-C}_8 \text{ alkyl, aryl, heteroaryl, } \text{C}_3\text{-C}_{10} \text{ cycloalkyl, or} \\ \text{C}_3\text{-C}_{10} \text{ (cycloalkyl optionally containing one, two, or three heteroatoms} \\ \text{selected from O, S, NH, or N alkyl); or R}_6 \text{ and R}_7 \text{ together with the} \\ \text{nitrogen to which they are attached complete a 3-10 member cyclic ring} \\ \text{optionally containing 1, 2, or 3 additional heteroatoms selected from O, S,} \\ \text{NH, or N alkyl;}\end{array}$$

15 and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, and the pharmaceutically acceptable salts thereof.

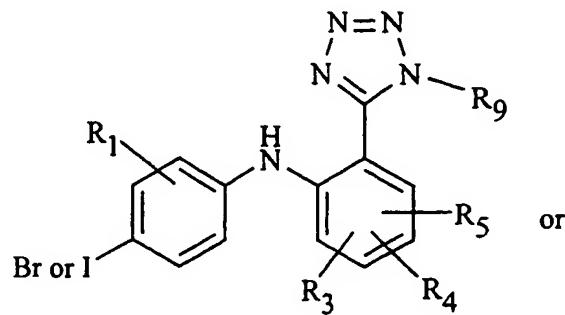
20 Preferred compounds have Formula II



where R₁, R₃, R₄, R₅, R₆, and R₇ are as defined above. Especially preferred are compounds wherein R₁ is methyl or halo, and R₃, R₄, and R₅ are halo such as fluoro or bromo.

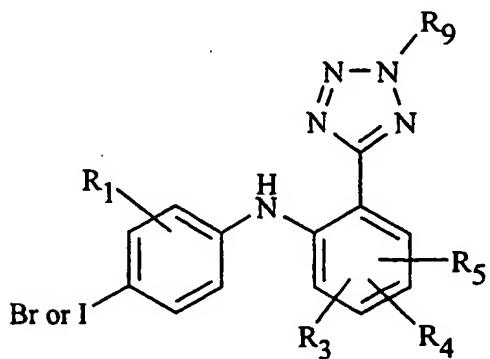
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The compounds of Formula II are carboxylic acids when R_7 is hydrogen, and are esters when R_7 is other than hydrogen. Compounds which are analogous to the acids in physical and biological properties are tetrazolyl derivatives of Formula IIa

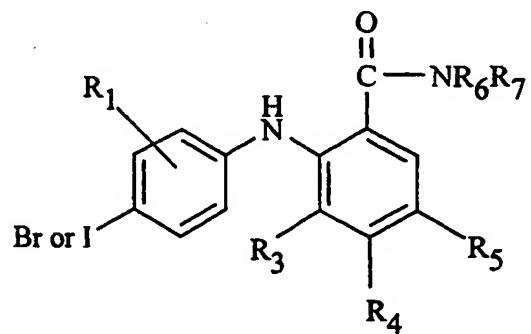


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IIa



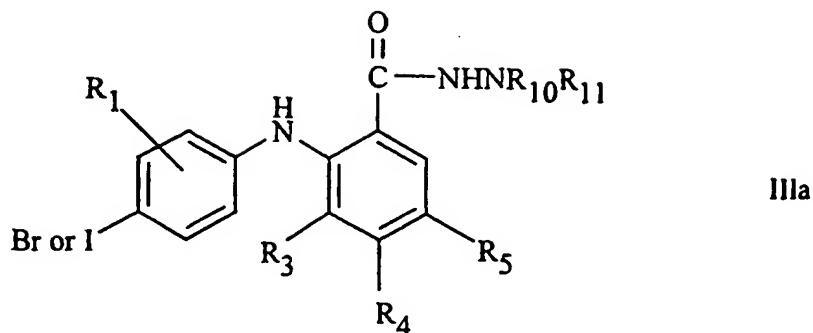
Another preferred group of compounds are amides Formula III



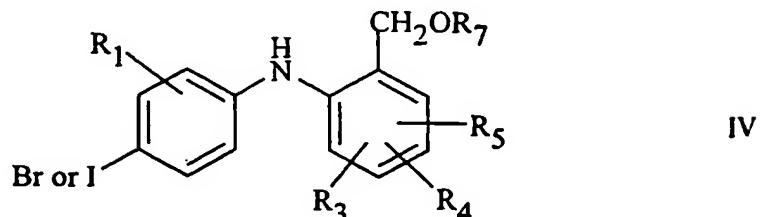
III

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and hydrazides of Formula IIIa

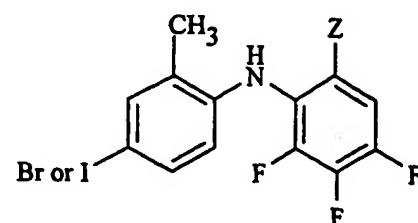
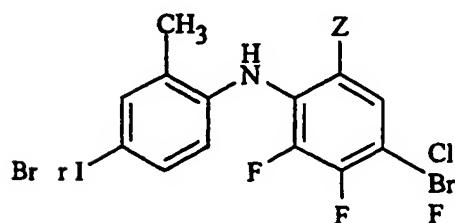
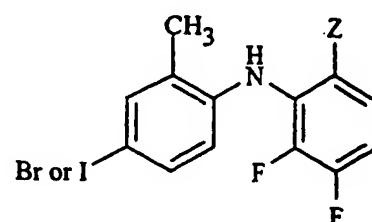
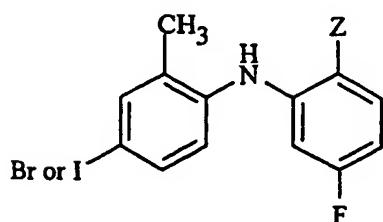


The benzyl alcohols of the invention have Formula IV



5

The most preferred compounds are those wherein R₁ is methyl, R₃ is hydrogen or halo such as fluoro, R₄ is halo such as fluoro, and R₅ is hydrogen or halo such as fluoro, bromo, or chloro. Representative compounds have the formulas



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This invention also provides pharmaceutical formulations comprising a compound of Formula I together with a pharmaceutically acceptable excipient, diluent, or carrier. Preferred formulations include any of the foregoing preferred compounds together with an excipient, diluent, or carrier.

5 The compounds of Formula I are potent and selective inhibitors of MEK₁ and MEK₂ kinase enzymes. They are, therefore, useful to treat subjects suffering from cancer, stroke, diabetes, Alzheimer's disease, cystic fibrosis, viral disease, heart failure, and proliferative diseases such as psoriasis, restenosis, autoimmune disease, and atherosclerosis. The compounds are especially well
10 suited to treat cancers such as breast cancer, colon cancer, prostate cancer, skin cancer, and pancreatic cancer. They are particularly well-suited for use in conjunction with conventional radiation therapy. The compounds are also immunomodulatory agents and can be used to treat degenerative diseases where change in MEK activation leads to pathologies such as hepatomegaly and
15 cardiomegaly. The invention provides a method of inhibiting MEK enzymes and the foregoing diseases by administering to a subject an effective amount of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "aryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from five to twelve carbon atoms. Examples of typical aryl groups include phenyl, naphthyl, and fluorenyl. The aryl may be substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Typical substituted aryl groups include 3-fluorophenyl, 3,5-dimethoxyphenyl, 25 4-nitronaphthyl, 2-methyl-4-chloro-7-aminofluorenyl, and the like.

The term "aryloxy" means an aryl group bonded through an oxygen atom, for example phenoxy, 3-bromophenoxy, naphthoxy, and 4-methyl-1-fluorenyloxy.

30 "Heteroaryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from four to eleven carbon atoms and one, two, or three heteroatoms

selected from O, S, or N. Examples include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, xanthenyl, pyronyl, indolyl, pyrimidyl, naphthyridyl, pyridyl, benzimidazolyl, and triazinyl. The heteroaryl groups can be unsubstituted or substituted by one, two, or three groups selected from fluoro, 5 chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Examples of substituted heteroaryl groups include chloropyranyl, methylthienyl, fluoropyridyl, amino-1,4-benzisoxazinyl, nitroisoquinolinyl, and hydroxyindolyl.

The heteroaryl groups can be bonded through oxygen to make 10 heteroaryloxy groups, for example thienyloxy, isothiazolyloxy, benzofuranyloxy, pyridyloxy, and 4-methoxyisoquinolinyl.

The term "C₁-C₈ alkyl" means straight and branched chain aliphatic groups having from one to eight carbon atoms, preferably one to four. Typical C₁-C₈ alkyl groups include methyl, ethyl, isopropyl, tert.-butyl, 15 2,3-dimethylhexyl, and 1,1-dimethylpentyl. The alkyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, as those terms are defined herein. Typical substituted alkyl groups include chloromethyl, 3-hydroxypropyl, 2-dimethylaminobutyl, and 2-(hydroxymethylamino)ethyl. Examples of aryl and 20 aryloxy substituted alkyl groups include phenylmethyl, 2-phenylethyl, 3-chlorophenylmethyl, 1,1-dimethyl-3-(2-nitrophenoxy)butyl, and 3,4,5-trifluorophenylmethyl. Examples of alkyl groups substituted by a heteroaryl or heteroaryloxy group include thienylmethyl, 2-furylethyl, 6-furyloxyoctyl, 4-methylquinoloxymethyl, and 6-isothiazolylhexyl. Cycloalkyl 25 substituted alkyl groups include cyclopropylmethyl, 2-cyclohexyethyl, piperidyl-2-methyl, 2-(piperidin-1-yl)-ethyl, 3-(morpholin-4-yl)propyl.

"C₂-C₈ Alkenyl" means a straight or branched carbon chain having one or 30 more double bonds. Examples include but-2-enyl, 2-methyl-prop-2-enyl, 1,1-dimethyl-hex-4-enyl, 3-ethyl-4-methyl-pent-2-enyl, and 3-isopropyl-pent-4-enyl. The alkenyl groups can be substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aryl, aryloxy, heteroaryl, or heteroaryloxy, for example

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2-bromoethenyl, 3-hydroxy-2-but enyl, 1-aminoethenyl, 3-phenylprop-2-enyl, 6-thienyl-hex-2-enyl, 2-furyloxy-but-2-enyl, and 4-naphthoxy-hex-2-enyl.

“C₂-C₈ Alkynyl” means a straight or branched carbon chain having from two to eight carbon atoms and at least one triple bond. Typical alkynyl groups include prop-2-ynyl, 2-methyl-hex-5-ynyl, 3,4-dimethyl-hex-5-ynyl, and 2-ethyl-but-3-ynyl. The alkynyl groups can be substituted as the alkyl and alkenyl groups, for example, by aryl, aryloxy, heteroaryl, or heteroaryloxy, for example 4-(2-fluorophenyl)-but-3-ynyl, 3-methyl-5-thienylpent-4-ynyl, 3-phenoxy-hex-4-ynyl, and 2-furyloxy-3-methyl-hex-4-ynyl.

10 The alkenyl and alkynyl groups can have one or more double bonds or triple bonds, respectively, or a combination of double and triple bonds. For example, typical groups having both double and triple bonds include hex-2-en-4-ynyl, 3-methyl-5-phenylpent-2-en-4-ynyl, and 3-thienyloxy-hex-3-en-5-ynyl.

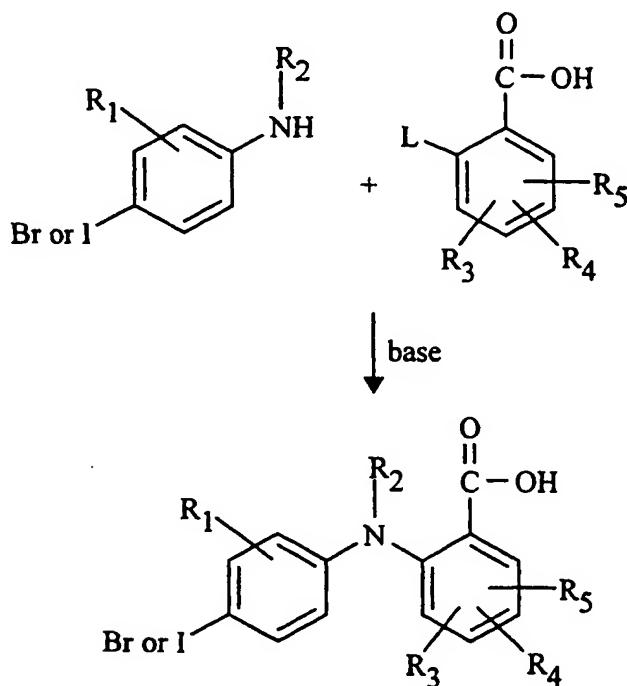
15 The term “C₃-C₁₀ cycloalkyl” means a nonaromatic ring or fused rings containing from three to ten carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, bicycloheptyl, adamantyl, and cyclohexyl. The ring can optionally contain one, two, or three heteroatoms selected from O, S, or NR₉. Such groups include tetrahydrofuryl, tetrahydropyrrolyl, octahydrobenzofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, 20 octahydroindolyl, and octahydrobenzothiofuranyl. The cycloalkyl groups can be substituted with the same substituents as an alkyl and alkenyl groups, for example, halo, hydroxy, aryl, and heteroaryloxy. Examples include 3-hydroxycyclohexyl, 2-aminocyclopropyl, 2-phenylpyrrolidinyl, and 3-thienylmorpholine-1-yl.

25 R₆ and R₇ can be taken together with the nitrogen to which they are attached to complete a cyclic ring having from 3 to 10 members, which may contain 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl. Examples of such cyclic rings include piperazinyl, piperidyl, pyrrolidinyl, morpholino, N-methylpiperazinyl, aziridinyl, and the like. Such rings can be substituted with halo, hydroxy, alkyl, alkoxy, amino, alkyl, and dialkylamino, 30 aryl, aryloxy, heteroaryl, and heteroaryloxy. Typical examples include 3-hydroxypyrrrolidinyl, 2-fluoro-piperidyl, 4-(2-hydroxyethyl)-piperidinyl, and 3-thienylmorpholino.

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The 2-(4-bromo and 4-iodo phenylamino)-benzoic acid derivatives of Formula I can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a 5 benzoic acid having a leaving group at the 2-position to give a 2-(phenylamino)-benzoic acid. This process is depicted in Scheme 1.

Scheme 1



where L is a leaving group, for example halo such as fluoro.

10 The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, triethylamine, and Hunig's base. The reaction generally is carried out at a 15 temperature of about -78°C to about 100°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the

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solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

The 2-(phenylamino)-benzoic acid (eg, Formula I, where R₇ is hydrogen) can be reacted with an organic or inorganic base such as pyridine, triethylamine, calcium carbonate, or sodium hydroxide to produce a pharmaceutically acceptable salt. The free acids can also be reacted with an alcohol of the formula HOR₇ (where R₇ is other than hydrogen, for example methyl) to produce the corresponding ester. Reaction of the benzoic acid with an alcohol can be carried out in the presence of a coupling agent. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP), and (benzotriazolyl) tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and alcohol derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

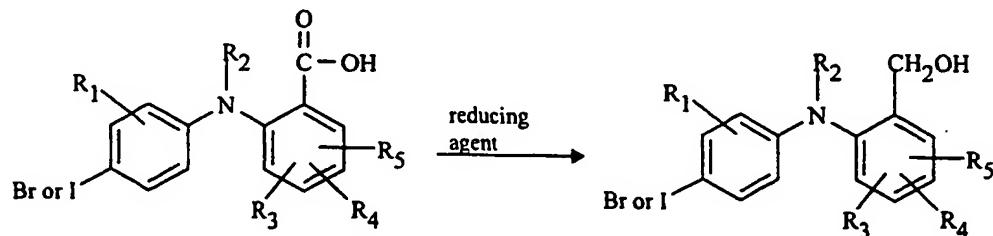
The benzamides of the invention, Formula I where Z is CONR₆R₇, are readily prepared by reacting the foregoing benzoic acids with an amine of the formula HNR₆R₇. The reaction is carried out by reacting approximately equimolar quantities of the benzoic acid and amine in an unreactive organic solvent in the presence of a coupling reagent. Typical solvents are chloroform, dichloromethane, tetrahydrofuran, benzene, toluene, and xylene. Typical coupling reagents include DCC, EEDQ, PyBrOP, and PyBOP. The reaction is generally complete after about 10 minutes to about 2 hours when carried out at a temperature of about 0°C to about 60°C. The product amide is readily isolated by

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removing the reaction solvent, for instance by evaporation, and further purification can be accomplished by normal methods such as chromatography, crystallization, or distillation. The hydrazides ($z = \text{CONHN}_1\text{R}_{11}$) are similarly prepared by coupling a benzoic acid with a hydrazine of the formula

5 $\text{H}_2\text{HNR}_{10}\text{R}_{11}$.

The benzyl alcohols of the invention, compounds of Formula I where Z is CH_2OR_6 and R_6 is hydrogen, are readily prepared by reduction of the corresponding benzoic acid according to the following scheme



10 Typical reducing agents commonly employed include borane in tetrahydrofuran. The reduction normally is carried out in an unreactive organic solvent such as tetrahydrofuran, and generally is complete within about 2 hours to about 24 hours when conducted at a temperature of about 0°C to about 40°C.

15 The following detailed examples illustrate specific compounds provided by this invention.

EXAMPLE 1

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

To a stirring solution comprised of 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) 20 of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethenylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which 25 temperature it was stirred for 2 days. The reaction mixture was concentrated.

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Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried (MgSO_4) and then boiled over a steambath to low volume and cooled to room temperature. The off-white fibers were collected by vacuum filtration, rinsed with hexanes, and vacuum-oven dried. (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

5 ^1H NMR (400 MHz; DMSO): Δ 9.72 (s, 1H), 7.97 (dd, 1H, J = 7.0, 8.7 Hz), 7.70 (d, 1H, J = 1.5 Hz), 7.57 (dd, 1H, J = 8.4, 1.9 Hz), 7.17 (d, 1H, J = 8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

10 ^{13}C NMR (100 MHz; DMSO): Δ 169.87, 167.60, 165.12, 150.17, 150.05, 139.83, 138.49, 136.07, 135.31, 135.20, 135.07, 125.60, 109.32, 105.09, 104.87, 99.72, 99.46, 89.43, 17.52;

^{19}F NMR (376 MHz; DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C = O stretch) cm^{-1} ;

15 MS (CI) $\text{M}+1$ = 372.

Analysis calculated for $\text{C}_{14}\text{H}_{11}\text{FINO}_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

EXAMPLES 2-30

20 By following the general procedure of Example 1, the following benzoic acids and salts were prepared:

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| Example No. | Compound | MP °C |
|----------------|---|-------------|
| 2 | 3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 206-210 |
| 3 | 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 240.5-244.5 |
| 4 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 259.5-262 |
| 5 | 5-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid | 255-260 |
| 6 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 234-238 |

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| Example No. | Compound | MP °C |
|-------------|--|-------------|
| 7 | Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate | 310-320 DEC |
| 8 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 239.5-240 |
| 9 | 2-(2-Chloro-4-iodo-phenylamino)-5-nitro-benzoic acid | 289-293 |
| 10 | 4-Fluoro-2-(3-fluoro-4-iodo-2-methyl-phenylamino)-benzoic acid | 233-235 |
| 11 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid | 264-267 |
| 12 | 2-(2-Fluoro-4-iodo-phenylamino)-5-nitro-benzoic acid | 256-258 |
| 13 | 2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid | 218.5-220 |
| 14 | 2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid | 285-288 DEC |
| 15 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid | 230-234 |
| 16 | 3-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 218-221 |
| 17 | 3,4-Difluoro-2-(4-iodo-2-methoxy-phenylamino)-benzoic acid | 230-233 |
| 18 | 4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 245-255 DEC |
| 19 | 2-(4-Iodo-2-methyl-phenylamino)-benzoic acid | 218-223 |
| 20 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 243-46 |
| 21 | 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 241-245 |
| 22 | 2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid | 218-222 |
| 23 | 4-Fluoro-2-(3-chloro-4-iodo-2-methyl-phenylamino)-benzoic acid | 248-252.5 |
| 24 | 2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid | 208-211 |
| 25 | 3-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid | 232-233 |
| 26 | 2-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid | 179-182 |
| 27 | 4-Fluoro-2-(2,3-dimethyl-4-iodo-2-methyl-phenylamino)-benzoic acid | 258-261 |
| 28 | 5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 209.5-211 |
| 29 | 2-Chloro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid | 171-175 |
| 30 | 2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid | 251-263 |

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EXAMPLE 31

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirring solution comprised of 0.1020 g (0.2632 mmol) of 5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid, 0.1 mL (1.7 mmol) of ethanolamine, and 0.05 mL (0.29 mmol) of diisopropylethylamine in 5 mL of a 1:1 (v/v) tetrahydrofuran-dichloromethane solution was added 0.15 g (0.29 mmol) of solid PyBOP powder directly. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The crude residue was partitioned between ether (50 mL) and 10% aqueous hydrochloric acid (50 mL). The organic phase was washed with 10% aqueous sodium hydroxide (50 mL), dried (MgSO_4) and concentrated in vacuo to afford a yellow-brown oil which was crystallized from hexanes-ether to afford 0.0831 g (73%) of a green-yellow powder; mp 120-121°C;

$^1\text{H NMR}$ (400 MHz; CDCl_3): δ 9.11 (s, 1H), 7.56 (d, 1H, J = 1.4 Hz), 7.46-7.41 (m, 2H), 7.20 (dd, 1H, J = 8.9, 2.4 Hz), 7.00 (t, 2H, J = 9.6 Hz), 6.55 (broad t, 1H), 3.86 (t, 2H, J = 5.0 Hz), 3.61 (dd, 2H, J = 10.1, 5.5 Hz), 2.23 (s, 3H), 1.56 (broad s, 1H);

IR (KBr) 3297 (O-H stretch), 1627 (C = O stretch) cm^{-1} ;

MS (Cl) $M+1 = 431$.

Analysis calculated for $\text{C}_{16}\text{H}_{16}\text{ClIN}_2\text{O}_2$:

C, 44.62; H, 3.74; N, 6.50.

Found: C, 44.63; H, 3.67; N, 6.30.

EXAMPLES 32-48

By following the general procedure of Example 31, the following benzamides were prepared by reacting the corresponding benzoic acid with the corresponding amine.

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| Example No. | Compound | MP °C |
|----------------|--|-------------|
| 32 | 4-Methoxy-N-(4-methoxy-phenyl)-3-nitro-benzamide | 153.5-156 |
| 33 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 158 |
| 34 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide | 102.5-104.5 |
| 35 | N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 90-91 |
| 36 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide | oil |
| 37 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide | 285-288 DEC |
| 38 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 180-182 |
| 39 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide | 137-138 |
| 40 | [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoyl]amino]-acetic acid | 170-173 |
| 41 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide | 69-71 |
| 42 | 5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 132-133.4 |
| 43 | N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | oil |
| 44 | 4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide | 122-124 |
| 45 | N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 91-93 |
| 46 | N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 97-99 |

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| Example No. | Compound | MP °C |
|----------------|--|-----------|
| 47 | 5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 118-120 |
| 48 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide | 142.5-144 |

EXAMPLE 49

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.50 g, 1.35 mmol) was dissolved in 6 mL (6 mmol) of cold 1.0 M borane-5 tetrahydrofuran complex in tetrahydrofuran solution. The reaction mixture was stirred under nitrogen atmosphere at room temperature overnight. The reaction was quenched with 80 mL of methanol. Concentration in vacuo produced a clear tan oil which was purified by MPLC. Elution with dichloromethane afforded 0.4285 g (89%) of a white solid; mp 99-100.5°C;

10 ¹H NMR (400 MHz; DMSO): δ 7.57 (d, 1H, J=1.7 Hz), 7.45 (dd, 1H, J=8.4, 1.9 Hz), 7.39 (s, 1H), 7.29 (t, 1H, J=7.5 Hz), 6.89 (d, 1H, J=8.4 Hz), 6.67-6.60 (m, 1H), 5.47 (t, 1H, J=5.5 Hz), 4.49 (d, 2H, 5.1 Hz), 2.14 (s, 3H);
IR (KBr) 3372 (O-H stretch) cm⁻¹;
MS (CI) M+1 = 358.

15 Analysis calculated for C₁₄H₁₃FINO:
C, 47.08; H, 3.67; N, 3.92.
Found: C, 47.17; H, 3.75; N, 3.72.

EXAMPLE 50-52

20 The following benzyl alcohols were prepared by the general procedure of Example 49.

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| Example No. | Compound | MP °C |
|-------------|--|-------------|
| 50 | [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol | 82-85 |
| 51 | [2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol | 126.5-128.5 |
| 52 | [5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol | 60.5-63.5 |

Several invention compounds of Formula I were prepared utilizing combinatorial synthetic techniques. The general procedure is as follows:

To a 0.8-mL autosampler vial in a metal block was added 40 μ L of a 0.5 M solution of the acid in DMF and 40 μ L of the reagent amine (2M solution in Hunig's base and 1 M in amine in DMF). A 0.5M solution of PyBrop was freshly prepared and 50 μ L were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm \times 25 cm, 5 μ M spherical silica, pore size 115 Å derivatized with C-18, the sample was eluted at 4.7 mL/min with a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes). Fractions were collected by monitoring at 214 nM. The residue was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield.

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EXAMPLES 53-206

The following compounds of Formula I were prepared by combinatorial methodology:

| Example No. | Compound | MS M-H |
|-------------|--|--------|
| 53 | 5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 510 |
| 54 | N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 462 |
| 55 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide | 577 |
| 56 | 3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 432 |
| 57 | N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 444 |
| 58 | 3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 446 |
| 59 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 564 |
| 60 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide | 571 |
| 61 | 4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 414 |
| 62 | 5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 551 |
| 63 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide | 580 |
| 64 | 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide | 501 |
| 65 | 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 485 |

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| Example No. | Compound | MS M-H |
|----------------|---|-----------|
| 66 | 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide | 493 |
| 67 | N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 473 |
| 68 | N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 460 |
| 69 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxyethyl)-benzamide | 384 |
| 70 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide | 483 |
| 71 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide | 495 |
| 72 | 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide | 513 |
| 73 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide | 480 |
| 74 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 467 |
| 75 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide | 453 |
| 76 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide | 557 |
| 77 | 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide | 479 |
| 78 | 2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide | 425 |
| 79 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide | 461 |
| 80 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide | 475 |
| 81 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide | 445 |
| 82 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxypropyl)-benzamide | 400 |

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| Example No. | Compound | MS M-H |
|-------------|--|-----------|
| 83 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 437 |
| 84 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide | 474 |
| 85 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide | 450 |
| 86 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide | 431 |
| 87 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide | 444 |
| 88 | 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide | 451 |
| 89 | 5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide | 557* |
| 90 | 5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide | 541* |
| 91 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide | 487 |
| 92 | 5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide | 601* |
| 93 | 5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 486* |
| 94 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide | 497* |
| 95 | (3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]- | 466 |
| 96 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 484* |
| 97 | 5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 530* |
| 98 | N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 518* |

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| Example No. | Compound | MS M-H |
|----------------|--|-----------|
| 99 | N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)-benzamide | 562* |
| 100 | [5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)- | 499 |
| 101 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid phenethyl ester | 501 |
| 102 | N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide | 568* |
| 103 | [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)- | 455 |
| 104 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl- benzamide | 460 |
| 105 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 528* |
| 106 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide | 542* |
| 107 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 468* |
| 108 | 5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 472* |
| 109 | N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 502* |
| 110 | 5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 445* |
| 111 | 5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 516* |
| 112 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide | 482* |
| 113 | 5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 489* |
| 114 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide | 556* |

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| Example No. | Compound | MS M-H |
|----------------|---|-----------|
| 115 | N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 529* |
| 116 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide | 500* |
| 117 | 5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 500* |
| 118 | 5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 514* |
| 119 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide | 512* |
| 120 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide | 509* |
| 121 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide | 544* |
| 122 | N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 470* |
| 123 | 5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 516* |
| 124 | N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 456* |
| 125 | 5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 429* |
| 126 | N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 484* |
| 127 | N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 511* |
| 128 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide | 544* |
| 129 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide | 523* |
| 130 | [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)- | 439 |

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| Example No. | Compound | MS M-H |
|----------------|--|-----------|
| 131 | 5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 558* |
| 132 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide | 484* |
| 133 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide | 496* |
| 134 | [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1- | 482 |
| 135 | N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 500* |
| 136 | [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid | 443 |
| 137 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide | 495* |
| 138 | N-(3-Dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 483* |
| 139 | N-(2-Diisopropylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 498* |
| 140 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester | 490 |
| 141 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester | 506 |
| 142 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester | 536 |
| 143 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-thiobenzoic acid S-benzyl ester | 503 |
| 144 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester | 476 |
| 145 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester | 492 |
| 146 | N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 409 |

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| Example No. | Compound | MS M-H |
|----------------|---|-----------|
| 147 | 5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 429 |
| 148 | 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 413 |
| 149 | N-Benzyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 475 |
| 150 | N-Benzyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 593* |
| 151 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide | 567 |
| 152 | 5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 473 |
| 153 | N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 521 |
| 154 | N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 440 |
| 155 | 2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide | 486 |
| 156 | 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 425 |
| 157 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 459 |
| 158 | N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 409 |
| 159 | N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 583 |
| 160 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide | 538 |
| 161 | N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 425 |
| 162 | N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 436 |
| 163 | 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 469 |

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| Example No. | Compound | MS M-H |
|-------------|--|-----------|
| 164 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 475 |
| 165 | 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide | 646 |
| 166 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide | 598 |
| 167 | N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 436 |
| 168 | 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide | 565 |
| 169 | N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 469 |
| 170 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide | 473 |
| 171 | N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 517 |
| 172 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 519 |
| 173 | N-Benzyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 502 |
| 174 | N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 559 |
| 175 | N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 517 |
| 176 | 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide | 581 |
| 177 | 2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide | 500 |
| 178 | 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 567 |
| 179 | N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 451 |
| 180 | 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 467 |
| 181 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide | 533 |

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| Example No. | Compound | MS M-H |
|----------------|--|-----------|
| 182 | 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 511 |
| 183 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide | 489 |
| 184 | N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 478 |
| 185 | N-Benzyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 538 |
| 186 | N-Benzyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 477 |
| 187 | 5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 431 |
| 188 | 5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 475 |
| 189 | 2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide | 488 |
| 190 | 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 477 |
| 191 | N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 523 |
| 192 | 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 425 |
| 193 | N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 427 |
| 194 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 461 |
| 195 | N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 442 |
| 196 | 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide | 415 |
| 197 | 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide | 472 |
| 198 | N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 411 |

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| Example No. | Compound | MS M-H |
|----------------|---|-----------|
| 199 | 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide | 540 |
| 200 | N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 438 |
| 201 | N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide | 411 |
| 202 | N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 585 |
| 203 | N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide | 472 |
| 204 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide | 601 |
| 205 | 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide | 522 |
| 206 | N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide | 438 |

* M+H

EXAMPLE 207

Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amineStep a: Preparation of 5-Chloro-2-fluoro-benzaldehyde

5 To a solution of 1-chloro-4-fluorobenzene (13.06 g, 0.1 mol) in THF (180 mL), at -78°C, LDA (2 M solution in THF, 50 mL, 0.1 mol) was added dropwise. After stirring at -78°C for 1.5 hours, DMF (8 mL) was added to the reaction mixture and allowed to warm up to room temperature overnight. The reaction mixture was partitioned between water and Et₂O. The Et₂O layer was dried (MgSO₄) and the solvent removed in vacuum to give 14.95 g (94%) yield of

10 crude aldehyde:

¹H NMR (CDCl₃): δ, 10.3 (s, -C(=O)H).

Step b: Preparation of 5-Chloro-2-fluoro-benzaldehyde oxime

A solution of 5-chloro-2-fluoro-benzaldehyde (10 g, 0.0631 mol), hydroxylamine hydrochloride (6.57 g, 0.0946 mol) and pyridine (8.3 mL,

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0.1010 mol) in EtOH (100 mL) was heated at 75°C (oil bath temperature) for 1 hour and the solvent removed under vacuum to give an oil. The oil was partitioned between water and CH₂Cl₂. The CH₂Cl₂ layer was dried (MgSO₄) and the solvent removed under vacuum to give crude aldoxime as a solid. The solid was purified by medium pressure liquid chromatography on silica. Elution with CH₂Cl₂ gave 4.87 g (28%) of the aldoxime as white solid: mp 95-97°C; Analysis calculated for C₇H₅NOFCl:

C, 48.44; H, 2.90; N, 8.07.

Found: C, 48.55; H, 2.69, N, 7.90.

10 Step c: Preparation of 5-Chloro-2-fluoro-benzonitrile

A solution of the 5-chloro-2-fluoro-benzaldehyde oxime (3.15 g, 0.0182 mol) in acetic anhydride (150 mL) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous NaHCO₃ (200 mL) solution. The mixture was extracted with Et₂O. The Et₂O layer was dried (K₂CO₃) and the solvent removed to give the product as an oily solid. The product was used without further purification in the next step.

Step d: Preparation of 5-(5-Chloro-2-fluoro-phenyl)-1H-tetrazole

A mixture of 5-chloro-2-fluoro-benzonitrile (2.84 g, 0.01823 mol), butanol (15 mL), sodium azide (1.543 g, 0.0237 mol), acetic acid (1.36 mL, 0.0237 mol) was refluxed for 24 hours. The reaction mixture was cooled to room temperature, additional 1.543 g sodium azide added, and the reaction mixture refluxed for additional 24 hours. After cooling to room temperature, Et₂O (100 mL) and 10% aqueous NaOH (200 mL) were added sequentially. The mixture was vigorously stirred. The aqueous layer was separated, cooled with ice-methanol bath (-15°C) and acidified to pH 1 with conc. HCl. A gray solid precipitated. The solid was dried in vacuum at 50°C to give 1.76 g (49%) of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole: mp partial melt at 110°C, complete melting at 124°C);
¹H (400 Mz, CDCl₃): δ 8.19-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.61-7.52 (m, 1H);

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^{13}C (100 Mz, CDCl_3): δ 159.00, 156.49, 140.88, 133.02, 132.93, 130.73, 129.23, 129.21, 129.08, 126.05, 118.96, 118.73, 114.50;
MS (CI) $M+1 = 199$ (100), $M = 198$ (6).

Step e: Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

5

To a solution of 2-methyl-4-iodoaniline (3.52 g, 0.0151 mol) in THF (25 mL) at -78°C, LDA (2 molar solution in THF, 11.33 mL, 0.02267 mol) was added dropwise. After stirring for 0.5 hours, a solution of 1-(tetrazol-5-yl)-2-fluoro-5-chlorobenzene (1.5 g, 0.00756 mol) in THF (15 mL) was added dropwise. The reaction was stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous conc. NH_4Cl solution and extracted with CH_2Cl_2 . The organic layer was dried (MgSO_4) and the solvent removed giving a crude product as an oil. The oil with $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2:\text{MeOH}$ (9.7:0.3) gave 1.5 g (48%) of the desired product:

10

15 mp 205-208;

^1H (400 Mz, DMSO): δ 9.13 (s, 1H), 8.00-7.99 (s, 1H), 7.69 (s, 1H), 7.55-7.52 (m, 1H), 7.43-7.40 (m, 1H), 7.12-7.05 (m, 1H), 2.24 (s, 3H);
 ^{13}C (100 Mz, CDCl_3): δ 141.87, 139.28, 138.88, 135.47, 133.71, 131.65, 128.15, 123.69, 121.94, 116.68, 87.79, 17.22;

20 MS (CI) $M+2 = 413$ (44), $M+1 = 412$ (85), $M = 411$ (100).

Analysis calculated for $\text{C}_{14}\text{H}_{11}\text{N}_5\text{ClI}\cdot 0.5\text{H}_2\text{O}$:

C, 39.97; H, 2.87; N, 16.65.

Found: C, 38.87, H, 2.77; N, 16.47.

The following tetrazole substituted phenylamines were prepared by
25 following the general procedure of Example 207.

EXAMPLE 208

(4-Iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine, mp 231°C (dec)

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EXAMPLE 209

[4-Nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine, mp 205-208°C.

The invention compounds are useful in treating cancer and other proliferative diseases by virtue of their selective inhibition of the dual specificity 5 protein kinases MEK₁ and MEK₂. The invention compound has been evaluated in a number of biological assays which are normally utilized to establish inhibition of proteins and kinases, and to measure mitogenic and metabolic responses to such inhibition.

EXAMPLES 210-224

10 Additional invention compounds which were prepared by the general methods described above are:

| Example No. | Compound | MP °C |
|-------------|---|-------------|
| 210 | 2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-4-(2-morpholin-4-yl-ethylamino)-5-nitro-benzoic acid | 239-241 DEC |
| 211 | 4-Amino-2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid | >270 |
| 212 | 2,4-Bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid | >265 DEC |
| 213 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzoic acid | 218-225 DEC |
| 214 | 2-(2,6-Difluoro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid | 247-249 |
| 215 | 2-(2-Chloro-4-iodo-phenylamino)-4-nitro-benzoic acid | 267-269 |
| 216 | 2-(2,4-Diiodo-phenylamino)-4-fluoro-benzoic acid | 260-261 |
| 217 | 2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-benzoic acid | 259-262 |
| 218 | 4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid | 215-217 |

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| Example No. | Compound | MP °C |
|-------------|--|-------------|
| 219 | 2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-benzoic acid | 242-247 |
| 220 | 5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid | 312.5-318 |
| 221 | 2,3,5-Trifluoro-6-(4-iodo-2-methyl-phenylamino)-4-(4-methyl-piperazin-1-yl)-benzoic acid methyl ester dihydrofluoride salt | 118-121 |
| 222 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-methyl-piperazin-1-yl)-benazmide | 214-217 DEC |
| 223 | 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid N',N'-dimethyl-hydrazide | 154-175 DEC |
| 224 | 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide | 153.5-156 |

Enzyme Assays

Cascade assay for inhibitors of the MAP kinase pathway

Incorporation of ^{32}P into myelin basic protein (MBP) was assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) and a glutathione S-transferase fusion protein containing p45MEK (GST-MEK). The assay solution contained 20 mM HEPES, pH 7.4, 5 10 mM MgCl_2 , 1 mM MnCl_2 , 1 mM EGTA, 50 μM $[\gamma-^{32}\text{P}]$ ATP, 10 μg GST-MEK, 0.5 μg GST-MAPK and 40 μg MBP in a final volume of 100 μL . Reactions were stopped after 20 minutes by addition of trichloroacetic acid and 10 filtered through a GF/C filter mat. ^{32}P retained on the filter mat was determined using a 1205 Betaplate. Compounds were assessed at 10 μM for ability to inhibit incorporation of ^{32}P .

To ascertain whether compounds were inhibiting GST-MEK or GST MAPK, two additional protocols were employed. In the first protocol, compounds

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were added to tubes containing GST-MEK, followed by addition of GST-MAPK, MBP and [γ -³²P]ATP. In the second protocol, compounds were added to tubes containing both GST-MEK and GST-MAPK, followed by MBP and [γ -³²P]ATP. Compounds that showed activity in both protocols were scored as MAPK 5 inhibitors, while compounds showing activity in only the first protocol were scored as MEK inhibitors.

In vitro MAP kinase assay

Inhibitory activity was also confirmed in direct assays. For MAP kinase, 1 μ g GST-MAPK was incubated with 40 μ g MBP for 15 minutes at 30°C in a 10 final volume of 50 μ L containing 50 mM Tris (pH 7.5), 10 μ M MgCl₂, 2 μ M EGTA, and 10 μ M [γ -³²P]ATP. The reaction was stopped by addition of Laemmli SDS sample buffer and phosphorylated MBP resolved by electrophoresis on a 15 10% polyacrylamide gel. Radioactivity incorporated into MBP was determined by autoradiography, and subsequently by excision of the bands followed by scintillation counting.

In vitro MEK assay

For evaluation of direct MEK activity, 10 μ g GST-MEK₁ was incubated with 5 μ g of a glutathione S-transferase fusion protein containing p44MAP kinase with a lysine to alanine mutation at position 71 (GST-MAPK-KA). This mutation 20 eliminates kinase activity of MAPK, so only kinase activity attributed to the added MEK remains. Incubations were 15 minutes at 30°C in a final volume of 50 μ L containing 50 mM Tris (pH 7.5), 10 μ M MgCl₂, 2 μ M EGTA, and 10 μ M [γ -³²P]ATP. The reaction was stopped by addition of Laemmli SDS sample 25 buffer and phosphorylated GST-MAPK-KA was resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into GST-MAPK-KA was determined by autoradiography, and subsequently by excision of the bands followed by scintillation counting. Additionally, an artificially activated MEK was utilized that contained serine to glutamate mutations at positions 218 and 222 (GST-MEK-2E). When these sites are phosphorylated, MEK activity is

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increased. Phosphorylation of these sites can be mimicked by mutation of the serine residues to glutamate. For this assay, 5 µg GST-MEK-2E was incubated with 5 µg GST-MAPK-KA for 15 minutes at 30°C in the same reaction buffer as described above. Reactions were terminated and analyzed as above.

5

Whole cell MAP kinase assay

To determine if compounds were able to block activation of MAP kinase in whole cells, the following protocol was used: Cells were plated in multi-well plates and grown to confluence. Cells were then serum-deprived overnight. Cells were exposed to the desired concentrations of compound or vehicle (DMSO) for 10 30 minutes, followed by addition of a growth factor, for example, PDGF (100 ng/mL). After a 5-minute treatment with the growth factor, cells were washed with PBS, then lysed in a buffer consisting of 70 mM NaCl, 10 mM HEPES (pH 7.4), 50 mM glycerol phosphate, and 1% Triton X-100. Lysates were clarified by centrifugation at 13,000 × g for 10 minutes. Five micrograms of the 15 resulting supernatants were incubated with 10 µg microtubule associated protein-2 (Map2) for 15 minutes at 30°C in a final volume of 25 µL containing 50 mM Tris (pH 7.4), 10 mM MgCl₂, 2 mM EGTA and 30 µM [γ -³²P]ATP. Reactions were terminated by addition of Laemmli sample buffer. Phosphorylated 20 Map2 was resolved on 7.5% acrylamide gels and incorporated radioactivity determined by autoradiography and subsequent excision of the bands followed by scintillation counting.

Immunoprecipitation and antiphosphotyrosine immunoblots

To determine the state of tyrosine phosphorylation of cellular MAP kinase, 25 cells were lysed, endogenous MAP kinase was immunoprecipitated with a specific antibody, and the resulting immunoprecipitate analyzed for the presence of phosphotyrosine as follows: confluent cells were serum-deprived overnight and treated with compounds and growth factors as described above. Cells were then scraped and pelleted at 13,000 × g for 2 minutes. The resulting cell pellet was resuspended and dissolved in 100 µL of 1% SDS containing 1 mM NaVO₄. 30 Following alternate boiling and vortexing to denature cellular protein, 900 µL

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RIPA buffer (50 mM Tris (pH 7.4), 150 mM NaCl, 1% Triton X-100, 0.1% deoxycholate, and 10 mM EDTA) was added. To this mixture was added 60 μ L agarose beads coupled with rabbit immunoglobulin G and 60 μ L Pansorbin cells in order to clear the lysate of nonspecific binding proteins. This mixture was 5 incubated at 4°C for 15 minutes then centrifuged at 13,000 \times g for 10 minutes. The resulting supernatant was transferred to fresh tubes and incubated with 10 μ L of a polyclonal antisera raised against a fragment of MAP kinase for a minimum of 1 hour at 4°C. Seventy microliters of a slurry of agarose beads coupled with protein G and protein A was added and the incubation continued for an additional 10 30 minutes at 4°C. The beads were pelleted by centrifugation at 13,000 \times g for 5 minutes and washed three times with 1 mL RIPA buffer. Laemmli sample buffer was added to the final bead pellet. This mixture was boiled for 5 minutes then 15 resolved on a 10% acrylamide gel. Proteins on the gel were transferred to a nitrocellulose membrane and nonspecific binding sites on the membrane blocked by incubation with 1% ovalbumin and 1% bovine serum albumin in TBST (150 mM NaCl, 10 mM Tris (pH 7.4), and 0.05% Tween 20). The membrane was then incubated with a commercially available antibody directed against phosphotyrosine. Antibody bound on the membrane was detected by incubation with 125 I-protein A, followed by autoradiography.

20 Cell Growth Assays

3 H-Thymidine incorporation

Cells were plated in multi-well plates and grown to near confluence. The media was then removed and replaced with growth media containing 1% bovine serum albumin. After 24-hour serum starvation, compounds and specific growth 25 factors were added and incubations continued for an additional 24 hours. During the final 2 hours, 3 H-thymidine was added to the medium. To terminate the incubations, the medium was removed and cell layers washed twice with ice-cold phosphate-buffered saline. After the final wash, ice-cold 5% trichloroacetic acid was added and the cells incubated for 15 minutes at room temperature. The 30 trichloroacetic acid solution was then removed and the cell layer washed three

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times with distilled water. After the final wash, the cell layer was solubilized by addition of 2% sodium dodecylsulfate. Radioactivity in this solution was determined by scintillation counting.

In 3T3-L1 adipocyte cells, in which the inhibition blocks MAPK activation by insulin with an IC_{50} of 3 μ M, the compound had no effect on the insulin stimulated uptake of radiolabeled 2-deoxyglucose, or on the insulin-stimulated synthesis of either lipid or glycogen at 10 μ M concentration. This demonstrates that the inhibitor shows selectivity between the mitogenic and metabolic effects of insulin, and demonstrates that the inhibitor will show less toxicity than an inhibitor which does not show this surprising selectivity.

Monolayer growth

Cells were plated into multi-well plates at 10 to 20,000 cells/mL. Forty-eight hours after seeding, compounds were added to the cell growth medium and incubation was continued for 2 additional days. Cells were then removed from the wells by incubation with trypsin and enumerated with a Coulter counter.

Growth in soft-agar

Cells were seeded into 35-mm dishes at 5 to 10,000 cells/dish using growth medium containing 0.3% agar. After chilling to solidify the agar, cells were transferred to a 37°C incubator. After 7 to 10 days growth, visible colonies were manually enumerated with the aid of a dissecting microscope.

Order of addition experiments established that the invention compounds are inhibiting MEK and not MAP kinase. Experiments looking at the phosphorylation of a kinase defective mutant of MAP kinase as substrate (so that there can be no autophosphorylation of the MAP kinase to complicate interpretation) confirms that the inhibitor inhibits MEK with an IC_{50} essentially identical to that produced in the cascade assay.

Kinetic analysis demonstrates that the invention compounds are not competitive with ATP. Thus, they do not bind at the ATP binding site of the enzyme, which is probably the explanation as to why these compounds do not

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show the nonspecific kinase inhibitory activity typical of most kinase inhibitors, which do bind at the ATP binding site and which are ATP competitive.

The in vitro and in vivo biological activity of several representative compounds of Formula I in the foregoing assays is presented in Table 1.

Table 1

| Compound of Example No. | In Vitro | | In Vivo (Cell Culture) | |
|----------------------------|--------------|---------------------|------------------------|---------------------|
| | % Inhibition | IC ₅₀ µM | % Inhibition | IC ₅₀ µM |
| 1 | | 0.019 | | |
| 2 | | 0.014 | | 3 |
| 3 | | 0.0111 | | 10 |
| 4 | | 0.005 | | 1 |
| 5 | | 0.066 | | |
| 6 | | 0.071 | | |
| 7 | | 0.072 | | |
| 8 | | 0.086 | | |
| 9 | | 0.097 | | |
| 10 | | 0.101 | | |
| 11 | | 0.128 | | |
| 12 | | 0.135 | | |
| 13 | | 0.178 | | |
| 14 | | 0.179 | | |
| 15 | | 0.194 | | |
| 16 | | 0.323 | | |
| 17 | | 0.434 | | |
| 18 | | 0.446 | | |
| 19 | | 0.524 | 50% at 30 µM | |
| 20 | | 0.557 | | |
| 21 | | 0.569 | | |
| 22 | | 1.581 | 30% at 30 µM | |
| 23 | | 1.588 | | |
| 24 | | 1.944 | | |
| 25 | | 2.363 | | |
| 26 | | 2.609 | 50% at 30 µM | |

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Table 1

| Compound of Example No. | In Vitro | | In Vivo (Cell Culture) | |
|----------------------------|--------------|---------------------|------------------------|---------------------|
| | % Inhibition | IC ₅₀ µM | % Inhibition | IC ₅₀ µM |
| 27 | | 2.269 | | |
| 28 | | 3.670 | | |
| 29 | | 5.331 | | |
| 30 | 105 | | | 10 |
| 31 | | 0.226 | | |
| 32 | | 0.028 | | |
| 33 | | 0.052 | | |
| 34 | | 0.098 | | |
| 35 | | 0.121 | | |
| 36 | | 0.129 | | |
| 37 | | 0.237 | | |
| 38 | | 0.412 | | |
| 39 | | 0.497 | | |
| 40 | | 0.651 | 30% at 30 µM | |
| 41 | | 0.872 | | |
| 42 | | 0.920 | | |
| 43 | | >1.000 | | |
| 44 | | 1.481 | | |
| 45 | | 1.755 | | |
| 46 | | 1.814 | | |
| 47 | | 1.911 | | |
| 48 | | 1.945 | | |
| 49 | | 0.418 | | 3 |
| 50 | | 0.179 | | |
| 51 | | 0.887 | | |
| 52 | | 2.346 | | |
| 53 | | 0.047 | | 0.54 |
| 54 | | 0.158 | | |
| 55 | | 0.114 | | |
| 57 | | 0.399 | | |
| 89 | | 0.186 | | |
| 89 | | 0.614 | | |

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Table 1

| Compound of Example No. | In Vitro | | In Vivo (Cell Culture) | |
|----------------------------|--------------|---------------------|------------------------|---------------------|
| | % Inhibition | IC ₅₀ μM | % Inhibition | IC ₅₀ μM |
| 90 | | 0.604 | | |
| 91 | | 2.071 | | |
| 92 | | 0.253 | | |
| 93 | | 0.521 | | |
| 95 | | 1.001 | | |
| 96 | | 0.374 | | |
| 100 | | 1.994 | | |
| 184 | | 0.278 | | |
| 186 | | 0.555 | | |
| 187 | | 0.561 | | |
| 188 | | 0.771 | | |
| 189 | | 0.859 | | |
| 190 | | 0.921 | | |
| 191 | | 1.355 | | |
| 192 | | 1.797 | | |
| 193 | | 2.902 | | |
| 194 | | 4.952 | | |
| 195 | | 12.831 | | |
| 208 | | 1.215 | | |
| 209 | | 1.372 | | |
| 211 | | >0.1 | | |
| 212 | | 0.034 | | |
| 213 | | 0.062 | | |
| 214 | | 0.303 | | |
| 215 | | 0.031 | | |
| 216 | | 1.000 | | |
| 217 | | >1.00 | | |
| 218 | | 0.051 | | |
| 219 | | 0.108 | | |
| 220 | | 0.029 | | |
| 221 | | 0.002 | | |

Table 1

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| Compound of Example No. | In Vitro | | In Vivo (Cell Culture) | |
|----------------------------|--------------|--------------------------|------------------------|--------------------------|
| | % Inhibition | IC ₅₀ μ M | % Inhibition | IC ₅₀ μ M |
| 222 | | 0.085 | | |
| 223 | | 0.043 | | |
| 224 | | 0.028 | | |

The invention compounds will be utilized to treat subjects suffering from cancer and other proliferative diseases, immunodeficiency, and certain degenerative diseases, and in need of treatment. The compounds are ideally suited to treating psoriasis, restenosis, autoimmune disease, and atherosclerosis. The 5 compounds will generally be utilized as a pharmaceutical formulation, in which the compound of Formula I is present in a concentration of about 5% to about 95% by weight. The compounds can be formulated for convenient oral, parenteral, topical, rectal, or like routes of administration. The compound will be formulated with common diluents, excipients, and carriers routinely utilized in medicine, for instance, with polyols such as glycerin, ethylene glycol, sorbitol 70; mono- and 10 difatty acid esters of ethylene glycol. Starches and sugars such as corn starch, sucrose, lactose, and the like, can be utilized for solid preparations. Such solid formulations can be in the form of tablets, troches, pills, capsules, and the like. Flavoring agents such as peppermint, oil of wintergreen, and the like can be 15 incorporated.

Typical doses of active compound are those that are effective to treat the cancer or other proliferative disorder afflicting the mammal. Doses will generally be from about 0.1 mg per kilogram body weight to about 500 mg per kilogram body weight. Such doses will be administered from one to about four times a day, 20 or as needed to effectively treat the cancer, psoriasis, restenosis, or other proliferative disorder.

A preferred method for delivering the invention compound is orally via a tablet, capsule, solution, or syrup. Another method is parenterally, especially via intravenous infusion of a solution of the benzopyran in isotonic saline or 5% 25 aqueous glucose.

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Following are typical formulations provided by the invention.

EXAMPLE 225

Preparation of 50-mg Tablets

| Per Tablet | | Per 10,000 Tablets |
|------------|---|--------------------|
| 0.050 g | 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid | 500 g |
| 0.080 g | lactose | 800 g |
| 0.010 g | corn starch (for mix) | 100 g |
| 0.008 g | corn starch (for paste) | 80 g |
| 0.002 g | magnesium stearate (1%) | 20 g |
| 0.150 g | | 1500 g |

The benzoic acid, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 600 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The granules are passed through a #8 screen and dried at 120°F. The dry granules are passed through a #16 screen. The mixture is lubricated with 1% magnesium stearate and compressed into tablets. The tablets are administered to a mammal for inhibiting MEK enzymes and treating restenosis, atherosclerosis, and psoriasis.

5

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EXAMPLE 226

Preparation of Oral Suspension

| Ingredient | Amount |
|---|--------|
| 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(methyl)-benzamide | 500 mg |
| Sorbitol solution (70% NF) | 40 mL |
| Sodium benzoate | 150 mg |
| Saccharin | 10 mg |
| Red dye | 10 mg |
| Cherry flavor | 50 mg |
| Distilled water qs ad | 100 mL |

The sorbitol solution is added to 40 mL of distilled water and the benzamide derivative is suspended therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 5 mg of the invention compound.

5 The syrup is administered to a mammal for treating proliferative disease, especially breast cancer and skin cancer.

EXAMPLE 227

Preparation of Parenteral Solution

10 In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 20.0 g of 4-fluoro-2-(4-bromo-2-methyl-phenylamino)-benzyl alcohol. The volume of the solution is adjusted to 1000 mL by addition of water for injection. The formulation is heat sterilized, filled into 50-mL ampoules each containing 2.0 mL (40 mg of 4-fluoro-2-(4-bromo-2-methyl-phenylamino)-benzyl), and sealed under nitrogen.

15 The invention compound thus formulated will be administered to a mammal in need of treatment for a proliferative disorder such as cancer, psoriasis, restenosis, atherosclerosis, autoimmune disease, and other immunodeficient diseases and degenerative disorders, at a rate and dose effective to treat the condition. An "antiproliferative amount" of an invention compound is that

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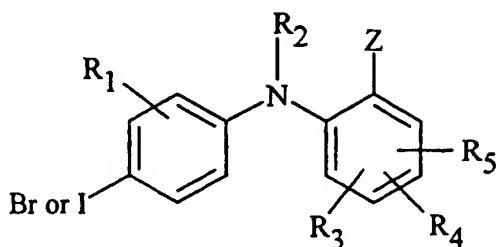
quantity of compound that inhibits or reduces the rate of proliferation of target cells. Typical cancers to be treated according to this invention include breast cancer, colon cancer, prostate cancer, skin cancer, and the like. The invention compound is especially well-suited for use in combination with radiation for 5 treating cancer. The compound is well-suited to the treatment of psoriasis, restenosis, and atherosclerosis, and to inhibiting the activity of MEK enzymes, especially MEK₁ and MEK₂. All that is required to inhibit these enzymes is to administer to a mammal an MEK inhibiting amount of a compound of the invention. An "MEK inhibiting amount" of an invention compound is an amount 10 that when administered to a mammal causes a measurable inhibition of the MEK enzyme. Typical MEK inhibiting amounts will be from about 0.1 μ g to about 500 mg of active compound per kilogram body weight. For treating the proliferative diseases mentioned above, typical doses will be from about 0.1 to about 50 mg/kg, normally given from one to about four times per day.

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CLAIMS

We claim:

1. The compounds of Formula I



1

5 wherein:

R₁ is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or CN;

R₂ is hydrogen;

R₃, R₄, and R₅ independently are hydrogen, hydroxy, halo,

10 trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, nitro, CN, or
-(O or NH)_m -(CH₂)_n-R₉, where R₉ is hydrogen, hydroxy,
COOH, or NR₁₀R₁₁;

n is 0-4;

m is 0 or 1;

15 R₁₀ and R₁₁ independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

20 Z is COOR₇, tetrazolyl, CONR₆R₇, CONHNR₁₀R₁₁, or CH₂OR₇;
R₆ and R₇ independently are hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl

C₂-C₈ alkynyl, C-C₁-C₈ alkyl, aryl, heteroaryl.

25 C₃-C₁₀ cycloalkyl, or C₃-C₁₀ (cycloalkyl optionally containing

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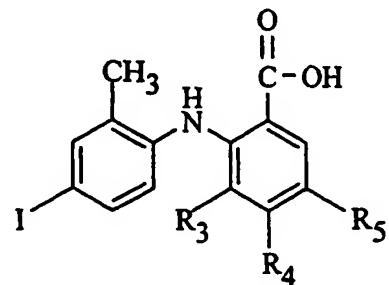
one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R₆ and R₇ together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl; and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, and the pharmaceutically acceptable salts thereof.

5 2. A compound according to Claim 1 wherein R₁ is CH₃ or halo.

10 3. A compound according to Claim 2 wherein Z is COOR₇, tetrazolyl, or a salt thereof.

15 4. A compound according to Claim 3 which is [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine; (4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine; and [4-Nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine.

20 5. A compound according to Claim 3 having the formula

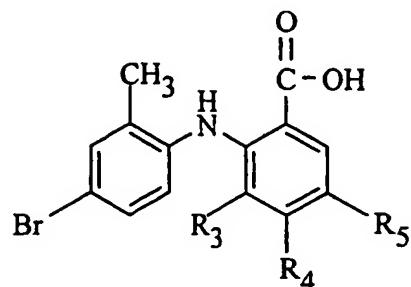


20 6. A compound of Claim 5 wherein R₃ is hydrogen, fluoro, or chloro; R₄ is hydrogen, fluoro, chloro, or nitro; and R₅ is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

7. A compound of Claim 6 which is
4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;
3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;
10 4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;
15 2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;
5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;
2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;
2,3,5-Trifluoro-6-(4-iodo-2-methyl-phenylamino)-4-(4-methyl-piperazin-1-yl)-
20 benzoic acid methyl ester dihydrofluoride salt;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-methyl-piperazin-1-yl)-benazmide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid N,N'-dimethyl-hydrazide; and
25 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide.

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8. A compound of Claim 3 having the formula



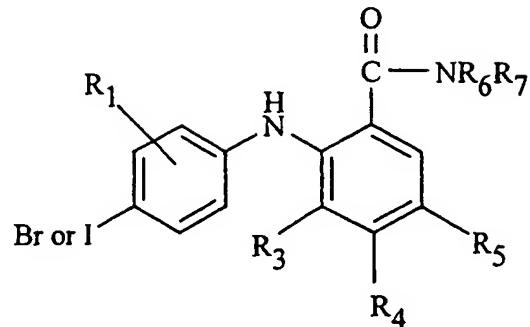
5 9. A compound of Claim 8 wherein R₃ is hydrogen, chloro, or fluoro; R₄ is hydrogen, chloro, fluoro, or nitro; R₅ is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

10 10. A compound of Claim 1 which is
2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;
2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;
2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-4-(2-morpholin-4-yl-ethylamino)-5-nitro-benzoic acid;
4-Amino-2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid;
2,4-Bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid;
2-(2-Chloro-4-iodo-phenylamino)-4-nitro-benzoic acid;
15 2-(2,4-Diiodo-phenylamino)-4-fluoro-benzoic acid;
2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-benzoic acid;
4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid;
2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-benzoic acid; and
5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid.

20 11. A compound of Claim 2 wherein Z is CONR₆R₇.

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12. A compound of Claim 11 having the formula



13. A compound of Claim 12 wherein R₃ is hydrogen, chloro, or fluoro; R₄ is

5 hydrogen, chloro, fluoro, or nitro; and R₅ is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

14. A compound of Claim 13 which is

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

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N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;
5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-
5 phenylamino)-benzamide;
N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-
1-yl-ethyl)-benzamide;
10 3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-
15 benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-
1-yl-ethyl)-benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-
4-yl-ethyl)-benzamide;
20 4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-
25 4-yl-ethyl)-benzamide;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-
ethyl)-benzamide;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-
ethyl)-benzamide;
30 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-
benzamide;
N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-
phenylamino)-benzamide;

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N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-
benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-
benzamide;
5 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-
benzamide;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-
propyl)-benzamide;
10 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-
benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-
benzamide;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-
ethyl)-benzamide;
15 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-
4-ylmethyl-benzamide;
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-
benzamide;
20 2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-
propyl)-3,4-difluoro-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-
benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-
benzamide;
25 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-
ethyl)-benzamide;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-
benzamide;
30 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-
ethyl)-benzamide;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;

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2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide;

5 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

10 5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide;

15 5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

20 (3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl];

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

25 N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

30 N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

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5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

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5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;
N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5
5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
10
N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
15
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;
[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-
20
(3-hydroxy-pyrrolidin-1-yl)-;
5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
25
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-
30
N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

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5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

10 N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

15 N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

20 N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

25 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide; 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

30 N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

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5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Benzyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

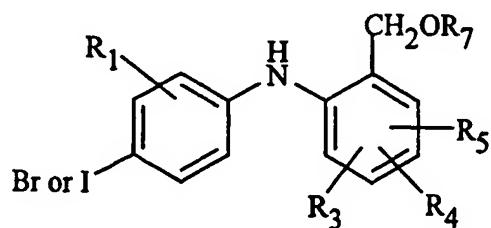
5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

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N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-
 benzamide;
 N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-
 5
 benzamide;
 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
 benzamide;
 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 10
 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-
 benzamide;
 N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;
 N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 N-Benzyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 15
 N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-
 benzamide;
 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-
 benzamide; and
 20
 N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

15. A compound of Claim 2 wherein Z is CH_2OR_7 .

16. A compound of Claim 15 having the formula



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17. A compound of Claim 16 wherein: R₃ is hydrogen, chloro, or fluoro; R₄ is hydrogen, chloro, fluoro, or nitro; and R₅ is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.
18. A compound of Claim 17 which is
5 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;
 [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;
 [2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol; and
 [5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol.
19. A pharmaceutical formulation comprising a compound of Claim 1 together
10 with a pharmaceutically acceptable excipient, diluent, or carrier.
20. A formulation of Claim 19 comprising a compound wherein Z is COOH or
 a salt thereof.
21. A formulation of Claim 19 comprising a compound wherein Z is
 CONR₆R₇.
- 15 22. A formulation of Claim 19 comprising a compound wherein Z is
 CH₂OR₇.
23. A method for inhibiting MEK enzymes in a mammal comprising
 administering an MEK inhibiting amount of a compound in Claim 1.
24. A method of treating a mammal suffering from a proliferative disease and
20 in need of treatment comprising administering an antiproliferative amount
 of a compound of Claim 1.
25. A method according to Claim 21 wherein the proliferative disease is
 psoriasis, restenosis, autoimmune disease, or atherosclerosis.

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26. A method according to Claim 21 wherein the proliferative disease is cancer.
27. A method for treating a mammal suffering from stroke and in need of treatment comprising administering an effective amount of a compound of 5 Claim 1.
28. A method for treating a mammal suffering from heart failure and in need of treatment comprising administering an effective amount of a compound of Claim 1.
29. A method for treating a mammal suffering from hepatomegaly and in need 10 of treatment comprising administering an effective amount of a compound of Claim 1.
30. A method for treating a mammal suffering from cardiomegaly and in need of treatment comprising administering an effective amount of a compound of Claim 1.
- 15 31. A method for treating a mammal suffering from diabetes and in need of treatment comprising administering an effective amount of a compound of Claim 1.
32. A method for treating a mammal suffering from Alzheimer's disease and 20 in need of treatment comprising administering an effective amount of a compound of Claim 1.
33. A method for treating a mammal suffering from cancer and in need of treatment comprising administering an effective amount of a compound of Claim 1 in combination with conventional radiation therapy.
34. A method for treating a mammal suffering from cystic fibrosis and in need 25 of treatment comprising administering an effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

onial Application No

PCT/US 98/13105

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C229/58 C07C237/30 C07C215/68 C07C243/38 C07D257/04
 C07D295/12 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| E | WO 98 37881 A (WARNER LAMBERT) 3 September 1998 see page 3, line 16 - page 14, line 31 see page 23, line 25 - page 53, line 4 see page 72, line 1 - page 79, line 30; claims 6,7 --- | 1-34 |
| X | BEKEMEIER H ET AL: "STRUCTURE-ACTIVITY RELATIONSHIP IN NONSTEROIDAL ANTIINFLAMMATORY AGENTS, INCLUDING OSAR IN FENAMATE DERIVATIVES" AGENTS AND ACTIONS SUPPLEMENTS, 1 July 1982, pages 17-34, XP002063635 see page 25, table I, compound 15; page 24, lines 16 to 28 --- | 1,19,20 -/- |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

21 October 1998

02/11/1998

Name and mailing address of the ISA

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Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

Int'l. Jpn. Application No

PCT/US 98/13105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | BERNER N H ET AL: "SUBSTITUTED N-PHENYLANTHRANILIC ACID HYDRAZIDES AS POTENTIAL ANTIMALARIAL AND ANTIMICROBIAL AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 13, no. 3, 1970, pages 552-554, XP002063637 see page 553, table I, compound 5; page 553, column 2 - 254, column 1 --- | 1,19,20 |
| X | R. M. ACHESON ET AL.: "The Condensation of Acridone with Tertiary Aromatic Amines and the Ultraviolet Absorption Spectra of the Products" JOURNAL OF THE CHEMICAL SOCIETY., 1956, pages 484-489, XP002081068 LETCWORTH GB see page 488, last two lines - page 489, middle --- | 1,2 |
| X | RAMANUJAM P ET AL: "ANTIFUNGAL ACTIVITY OF SOME N-SUBSTITUTED ANTHRANILIC ACID DERIVATIVES" PLANTA MEDICA, vol. 25, no. 1, 1974, pages 43-46, XP002063636 see page 44, table I, compound 6 --- | 1 |
| X | US 2 077 249 A (FRITZ MIETZSCH ET AL.) 13 April 1937 see page 2, column 2, line 21 - line 26 --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 99, no. 19, 7 November 1983 Columbus, Ohio, US; abstract no. 158369f, M. KHALIFA ET AL.: "Synthesis and Biological Activity of Certain Derivatives of 2,4-Dioxo-1,2,3,4-tetrahydroquinazoline" page 613; column 2; XP002081073 see abstract & EGYPT. J. CHEM., vol. 25, no. 3, 1983, pages 285-291, --- | 1,2 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/13105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | <p>CHEMICAL ABSTRACTS, vol. 77, no. 19, 6 November 1972 Columbus, Ohio, US; abstract no. 122522g, I. S. SHUL'GA ET AL.: "Synthesis of 6-Nitrodiphenylamine-2-carboxylic acid Derivatives, their Physicochemical and Antimicrobial Properties" page 65; column 1; XP002081074 see abstract & FARM. ZH., vol. 27, no. 3, 1972, pages 84-85, kiev</p> <p>---</p> | 1 |
| X | <p>CHEMICAL ABSTRACTS, vol. 114, no. 19, 13 May 1991 Columbus, Ohio, US; abstract no. 184706m, A. N. GAIDUKEVICH ET AL.: "Reactivity of Derivatives of Phenylanthranilic Acid. VII. Acid-base Properties of Derivatives of Phenylanthranilic Acid in Binary Solvent Dioxane-Water" page 714; column 1; XP002081075 see abstract -& CHEMICAL ABSTRACTS 12TH COLLECTIVE INDEX., vol. 106-115, 1987 - 1991, page 14641cs XP002081069 COLUMBUS US see column 2, line 44 - line 47 & ORG. REACT. TARTU), vol. 27, no. 1-2, 1990, pages 87-96,</p> <p>---</p> | 1 |
| X | <p>CHEMICAL ABSTRACTS, vol. 109, no. 17, 24 October 1988 Columbus, Ohio, US; abstract no. 149000b, I. S. SHUL'GA ET AL.: "Synthesis and Physicochemical and Biological Properties on Diphenylamine-2-carboxylic Acid Derivatives" page 682; column 1; XP002081076 see abstract -& CHEMICAL ABSTRACTS 12TH COLLECTIVE INDEX., vol. 106-115, 1987 - 1991, page 15109cs XP002081070 COLUMBUS US see column 2, line 38 - line 41 & FARM. ZH. (KIEV), no. 1, 1988, pages 42-45,</p> <p>---</p> | 1 |

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 98/13105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | <p>CHEMICAL ABSTRACTS, vol. 101, no. 3, 16 July 1984 Columbus, Ohio, US; abstract no. 22893z, V. I. MAKURINA ET AL.: "A Study of Acid-base Equilibria in Aqueous Dioxane Solutions of Phenanthranyl Acid Derivatives" page 549; column 2; XP002081077 see abstract -& CHEMICAL ABSTRACTS 11TH COLLECTIVE INDEX., vol. 96-105, 1982 - 1986, page 10688cs XP002081071 COLUMBUS US see column 2, line 12-14 see column 2, line 23 - line 25 see column 2, line 34 - line 39 & ORG. REACT (TARTU), vol. 20, no. 3, 1983, pages 311-315, ----</p> | 1 |
| X | <p>CHEMICAL ABSTRACTS, vol. 83, no. 3, 21 July 1975 Columbus, Ohio, US; abstract no. 27831x, JACEK ROMANOWSKI ET AL.: "Use of 2,6-Dichlorobenzonitrile (Dichlobenil) as a Starting Substance for Synthesizing Herbicides Derived from Benzoic Acid" page 473; column 1; XP002081078 see abstract -& CHEMICAL ABSTRACTS 9TH COLLECTIVE INDEX., vol. 76-85, 1972 - 1976, page 6385cs XP002081072 COLUMBUS US see column 3, line 28 - line 29 & PRZEM. CHEM., vol. 54, no. 1, 1975, pages 26-31, warsaw, poland ----</p> | 1 |
| A | <p>US 5 525 625 A (ALEXANDER J. BRIDGES ET AL.) 11 June 1996 see the whole document -----</p> | 1-34 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/13105

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 23-34
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 23-34
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/US 98/13105

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|--|------------------|
| WO 9837881 | A 03-09-1998 | NONE | | |
| US 2077249 | A 13-04-1937 | NONE | | |
| US 5525625 | A 11-06-1996 | AU 690400 B | | 23-04-1998 |
| | | AU 4245696 A | | 14-08-1996 |
| | | CA 2208075 A | | 01-08-1996 |
| | | EP 0805807 A | | 12-11-1997 |
| | | WO 9622985 A | | 01-08-1996 |

